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Sevuparin in children with severe malaria: A phase I safety and dose finding trial

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Abstract

Introduction:

Mortality rates for African children with severe malaria remain high. Sevuparin, a heparin-like compound, as an adjunctive treatment, may improve outcomes due to its effects on *Plasmodium falciparum*-infected erythrocytes.

Methods

A Phase I dose-finding trial in Kenyan and Zambian children hospitalised with severe malaria aimed to identify the maximum tolerated dose (MTD) of sevuparin, given as three infusions (at 0, 8 and 16 hours post-enrolment) using the continual reassessment method. Safety was assessed as dose limiting toxicity (DLT) defined as Activated Partial Thromboplastin Time (APTT) > 95 seconds (2.5x upper limit of normal) across 1.5-6mg/kg doses. Children were followed for 28 days. Grade 3 or 4 serious adverse events were recorded. Secondary endpoints were lactate clearance, parasite half-life, and APTT at 24 hours.

Results

Twenty-three children were enrolled; 20 were included in the primary analysis, across 10 cohorts. A data monitoring committee followed model recommendations, leading to dose escalation from 1.5mg/kg through all doses to 6mg/kg when 2 DLTs occurred. During de-escalation, DLTs occurred at 5mg/kg and 4mg/kg. The final dose was therefore 3mg/kg. There was 1 death (1/23 (4.3%)), 1 readmission and 1 grade 3 non-DLT adverse event: all judged unrelated to sevuparin.

Conclusion

MTD of 3mg/kg sevuparin in each of three infusions at 0, 8 and 16 hours was identified for future investigation.

Introduction

Malaria remains a key cause of paediatric hospital admission in sub-Saharan Africa and makes a substantial contribution to under 5-year mortality, estimated at ~ 600,000 annually[1,2]. In 2023, about 94% of *Plasmodium falciparum* malaria cases and 95% of global deaths occurred in the WHO African region[2]. Despite the widespread use of fast-acting artemisinin-based combination therapies, inpatient mortality for severe malaria remains unacceptably high at ~ 7–8% (shown in Akech et al, 2020[3] and SMAART Observational study ISRCTN14711763 (unpublished)) and will not improve without better supportive

treatments. Indeed, in children with the severest manifestation of cerebral malaria, namely deep unarousable coma, mortality of ~ 20–25% has largely remained unchanged over the decades[3,4] or by the introduction of artesunate[5]. The most promising vaccines, RTS,S (3 dose plus booster) and R21, offered short-term protection against uncomplicated malaria[6], but their effects on severe malaria and mortality have not yet been fully evaluated[7]. Clinical trials investigating the safety and efficacy of supportive treatments could fill existing gaps in the severe malaria treatment algorithm and substantially improve outcomes[8]. Yet, the paucity of clinical trial data is stark: only 33 clinical trials of supportive therapies have been conducted globally over the last 40 years, mostly single-centre Phase I or II trials involving few participants; none showed benefit[9], and several were stopped early for harm[10]. This is despite the fact that, in the recent past, over a million African children were dying from malaria annually[11].

Plasmodium falciparum parasite-infected erythrocytes (iRBC) have the unique ability to cytoadhere both to both endothelia[12] and to uninfected red cells (rosetting)[13], and to cause sequestration of iRBC and RBC in the microvasculature, which is central to the pathology of severe malaria. Autopsy studies have shown intense sequestration in vital organs in children and adults who have died from malaria[14,15] and most paediatric deaths from severe malaria in African hospitals occur soon after admission[5]. Supportive treatments that can reverse sequestration rapidly could therefore substantially improve survival in children admitted to hospital with severe malaria.

Heparin was previously investigated as an adjunctive treatment, hypothesised to reverse iRBC sequestration *in vivo* as it binds to *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), the key parasite adhesion molecule mediating sequestration[16,17]. Furthermore, heparin blocks merozoite invasion into red blood cells in vitro[18], a vital part of the malaria cycle of amplification of parasite load. However, clinical trials of heparin gave variable results, with some showing reduced mortality in children with severe *P. falciparum* malaria[19,20], some showing no clinical improvements when given at low dose[21] and others demonstrating potentially dangerous effects on coagulation[22]. Sevuparin is a low-anticoagulant heparin-like compound that is devoid of the negative effects of heparin on coagulation. It is a heparin derivative which is chemically modified so that the specific pentasaccharide domain responsible for high-affinity binding to antithrombin III is eliminated[23]. It therefore no longer includes the specific binding sequence for antithrombin, the main contributor to prolonged coagulation. As a result, sevuparin has no direct effect on factor Xa or thrombin, and its effect on activated partial thromboplastin time (APTT) is markedly reduced in comparison to standard dose heparin[24]. Like heparin, sevuparin binds to PfEMP1, reversing iRBC adhesion[25,26] and rosetting unblocking the microvasculature and restoring normal blood flow.

In a Phase I dose escalation trial in adults, sevuparin was shown to be safe and well-tolerated with minimal effects on APTT at doses of 1.5 mg/kg and 3mg/kg every six hours, but a dose of 6.0 mg/kg led to higher APTT values[27]. The subsequent Phase II trial conducted in adults with uncomplicated *P. falciparum* malaria compared sevuparin 6-hourly intravenous infusions over 5 minutes versus standard

treatment alone (control). There were minimal and non-clinically relevant changes in anti-Xa and prothrombin times and the international normalized ratios (INR) with sevuparin[27]. Increases in APTT were dose-dependent and appeared to follow the time-concentration curve for each sevuparin infusion. The 6-hour interval between infusions allowed for nearly full reversibility of APTT increases after each dose. No adverse effects were reported. Sevuparin has also been studied in children and adults for the treatment of acute vaso-occlusive crisis in patients with sickle cell disease (and has been granted Orphan Drug Designation and Rare Pediatric Disease Designation by the FDA for this indication). A Phase II trial in this population demonstrated that it was safe and well-tolerated but it did not prevent the initiation of vaso-occlusive crises[28].

We therefore hypothesised that in African children hospitalized with severe malaria, sevuparin would improve microcirculatory flow by reversing existing and preventing further parasite sequestration and hence reduce plasma lactate concentrations, a biomarker marker associated with poor outcomes directly linked to the degree of impaired perfusion[29]. However, testing this hypothesis, it is first essential to confirm the most appropriate sevuparin dose in children, the objective of this Phase I trial.

Results

Between 1st September 2022 and 5th Mar 2025, 23 children in Kenya and Zambia were enrolled and followed up to Day 28 (Fig. 1). 3 children enrolled in Kenya were excluded from analyses as APTT measurements were not available and they therefore could not be included in the continual reassessment model. Baseline clinical and laboratory features are summarised in Table 1 (20 children included in the primary analysis), and **Table S1** (all 23 children). In the 20 children included in the primary analysis the median age was 35 months (IQR 24, 48) and 12 (60%) were female. 10 (50%) children had unrousable coma (cerebral malaria; Blantyre Coma Score ≤ 2); median haemoglobin was 5.2mg/dl (IQR 4.6, 6.3): 3 (15%) had severe malarial anaemia (defined as <4g/dl); and 7 (35%) had deep ‘acidotic’ breathing. Median lactate was 3.5 mmol/l (IQR 2.6, 6.6).

Table 1
Baseline characteristics

Age (months)	**N (%) or median (IQR)**
	35 (24, 48)
Aged < 1 year	2 (10%)
Gender: Female	12 (60%)
Axillary temperature (°C)	37.5 (37.1, 38.3)
Blantyre Coma Score	
1	3 (15%)
2	7 (35%)
3	7 (35%)
4	2 (10%)
5	1 (5%)
Two or more seizures in last 24h	8 (40%)
Did the seizures last > 30mins?	2 (25%)
Hemoglobinuria	2 (10%)
Neck stiffness	1 (5%)
Deep breathing	7 (35%)
Haemoglobin (g/dL)	5.2 (4.6, 6.3)
Haemoglobin<4g/dl	3 (15%)
Lactate (mmol/L)	3.5 (2.6, 6.6)
Glucose (mmol/L)	6.3 (4.4, 8.6)
Parasite density (/µL)	174048 (48360, 432056)
APTT (seconds)	38.5 (36.4, 43.0)
Already received IV antimalarials	11 (55%)
Already received oral antimalarials	10 (50%)
N (%) or median (IQR). APTT = Activated Partial Thromboplastin Time	

Adherence to dosage

Following the protocol, all children in the dose escalation cohorts adhered to recommended dosage, or stopped subsequent dosages due to the development of a dose limiting toxicity (DLT), defined as Activated Partial Thromboplastin Time (APTT) > 95 seconds (2.5x upper limit of normal). As planned for the continual reassessment model, the first cohort of 4 children received each sevuparin infusion (given over 5 minutes) at 0, 8 and 16 hours after enrolment starting at 1.5 mg/kg per dose; followed by an escalation through 3 mg/kg, 4 mg/kg, 4.5 mg/kg, 5 mg/kg and 6 mg/kg in cohorts of 2 children each following the model's recommendations. Only at the 6 mg/kg dosage, after 14 children had been enrolled, were two DLT noted. The Data Monitoring Committee (DMC) recommended a reduction to 5 mg/kg for the next cohort (n = 2) following the model's recommendation. At the 5mg/kg dose both children had a DLT; this was followed by a recommendation to de-escalate to 4 mg/kg for the next cohort (n = 2) (skipping the 4.5mg/kg dose level) and both children at 4mg/kg developed DLT. The DMC recommended to deescalate to 3mg/kg for the final cohort (n = 2) following the model's recommendation and no DLT were reported **(**Fig. 2, **Table S2)**.

Primary Endpoint

The recorded APTT levels over 24 hours for individual children at each dosage are presented in Fig. 3. 6 (30%) children had DLT: 2 in each of the three doses of 4, 5 and 6 mg/kg. Most APTTs recorded as DLTs were in the range between > 95 and < 110 seconds. Only one child (who received 5 mg/kg) had an APTT > 110 seconds. DLT were recorded at 1 hour (n = 2), and at 9 hours (one hour post 2nd dose; n = 4); none were recorded at 24 hours (8 hours post 3rd dose). At 24 hours, the overall mean APTT was 36s (sd 13.2) **(**Table 2**)**. There were no adverse clinical events related to the DLT including no indication of any bleeding in any child.

Table 2
Outcomes and Adverse Events

Outcome	Dose level (mg/kg)						Total
	1.5	3	4	4.5	5	6	
	N = 4	N = 4	N = 4	N = 2	N = 4	N = 2	N = 20
Efficacy outcomes							
Change in lactate at 8 hrs (mmol/L)[a]	-0.6 (1.6)	-0.3 (2.9)	-1.8 (1.8)	-0.7 (-)	-7.1 (2.5)	-1.1 (-)	-1.9 (3.1)
Change in lactate at 24 hrs (mmol/L)[a]	1.0 (1.7)	-1.3 (2.2)	-1.8 (1.4)	-1.5 (-)	-7.4 (3.7)	-1.2 (-)	-1.9 (0.6)
Parasite half-life (hours) (geometric mean)	_[b]	_[b]	4.2 (N = 2)	11.1 (N = 1)	8.2 (N = 1)	5.0 (N = 1)	6.0 (3.5,10.4)[c]
Presence of mature infected erythrocytes at 8 hours	0	0	0	0	0	0	0
Presence of mature infected erythrocytes at 24 hours	0	0	0	0	0	0	0
Safety outcomes							
APTT at 24 hrs	43.1 (14.5)	29.9 (8.7)	38.4 (22.3)	31.7 (-)	34.2[d] (-)	36.5 (-)	36.0 (13.2)
Neurological sequalae at day 28	0	0	0	0	0	0	0
Adverse events*							
Deaths	0	0	0	0	1	0	1
Non-fatal SAES by day 28	0	0	1	0	0	0	1
Adverse events grade 3 or 4 by day 28	0	0	2	0	3	2	7

Outcome	Dose level (mg/kg)						Total
	1.5	3	4	4.5	5	6	
Arithmetic mean (sd) or N (%) presented unless specified otherwise. Standard deviation not shown when N < 4.							
[a] One child died prior to the 24 hour measurement of lactate (in the 5mg/kg dose). Two children (1 in the 4.5mg/kg dose and 1 in the 5mg/kg dose) did not have a lactate measured within the window around 8 hours.							
[b]Not estimated as ≤ 2 measurements in each child							
[c] 95% confidence interval presented around geometric mean							
[d] One child died prior to the 24 hour measurement of APTT.							
*A dose limiting toxicity of APTT > 2.5xULN was also a grade 3 adverse event and 2/2 events in dose level 4, 2/3 events in dose level 5 and 2/2 events in dose level 6 were dose limiting toxicities. These were deemed possibly or probably related to sevuparin. The other adverse event at the dose of 5 mg/dg was a grade 3 clinical event (fever and cough), unlikely related to sevuparin. The non-fatal SAE was a hospital readmission due to anaemia and unlikely related to sevuparin. The death due to complicated malaria was judged unlikely related to sevuparin.							

Secondary Endpoints

The overall change in lactate in the window around 8 hours (5–12 hours) was a mean reduction of 1.9mmol/L (sd 3.1; measured on 18/20 children); at 24 hours the decrease was also 1.9mmol/L (sd 0.6; measured on 19/20 children). Parasite clearance half-life could only be estimated in 5/20 children since this required 3 measurements of slide parasitaemia; 10/15 children in whom this could not be calculated were only slide positive at baseline and 9 hours and 5/15 children were slide positive only at baseline. In the 5 children in whom this could be calculated, the overall geometric mean parasite half-life was 6 hours (95%CI 3.5–10.4 hours). There were no mature infected erythrocytes (schizonts) seen on microscopy at 9 or 24 hours.

Safety and other exploratory endpoints

In the 20 children included in the primary analysis, there were 7 grade 3 adverse events of which 6 were the laboratory-defined DLTs without clinical complications described above. The additional grade 3 adverse event was a high fever and cough. By intention to treat in the 23 children enrolled there was one non-fatal serious adverse event (hospital readmission for anaemia) and one death due to complications of malaria, judged unlikely to be related to sevuparin by the clinical team and on independent review. There were no neurological sequalae reported at the day 28 visit.

An additional analysis of primary, secondary and safety endpoints of all children (including those without APTT measures) gave similar results (**Table S3**). There was only one additional adverse event which was a hospital readmission for convulsions.

In children with lactate measurements, 5/18 (28%) had lactate ≤2mmol/L in the window around 8 hours, and 7/19 (37%) at 24 hours (**Figure S1**).

Discussion

Through this small Phase I single arm trial, we have confirmed a paediatric dose, and ascertained further evidence on the safety of sevuparin given as an adjunctive therapy alongside intravenous artesunate. All APTT dose limiting toxicities were clinically silent. In the primary analysis population, the only other adverse events reported were one grade 3 fever and cough and two serious adverse events (one death and one readmission), all judged unlikely to be related to sevuparin. We established, using the continual reassessment method, the maximum tolerated dose of sevuparin of 3mg/kg in children hospitalised with severe malaria. This is similar to the dose recommended for future investigation in the adult trial Phase I trial[27]. We demonstrated early lactate clearance (to < 2mmol/l) in 28% children by 8 hours and that 15/20 (75%) children had cleared their parasitaemia by 24 hours. Of note, the observed overall mortality rate in the 23 children enrolled (4%, 95% CI 0.1–21%) was much lower than expected given that 50% of the children in the trial had the severest clinical presentation of unrousable coma (cerebral malaria) and metabolic acidosis (lactate > 2 mmol/l). We used the PET score[30] to predict expected mortality, a score developed from the FEAST trial data and validated in external data sets to assess risk of mortality from baseline clinical variables. The majority (19/20) of the children in this study had scores ≥ 5 putting them at ≥ 10% risk of mortality (**Figure S3** and **Table S4**). Furthermore, mortality rates to Day 28 in children included in SMAART observation study (conducted 2022–2024) who presented in coma complicated by metabolic acidosis (lactate > 2 mmol/l) were 24/70 (34%) in Nchelenge, Zambia and 4/19 (21%) in Kilifi, Kenya (personal communication).

One of the strengths of the trial is the excellence adherence to dosing strategy (100%); in those with valid measures of APTT (20/23) there was 100% compliance to DLT stopping rules and similar completeness to follow up and ascertainment of survival status. Operationally the conduct of the trial teams through planned recruitment pauses following completion of each dosage cohort, timely analysis to update the models recommendation for the next dosage and rapid review by the independent DMC was of high quality and carried out closely following the protocol.

The limitations included the paucity of laboratory measures of severity at baseline (including biomarkers assessing renal function and quantification of parasite biomass (*Pf*HRP2 measurement) and less frequent measurements of parasitaemia on blood films than recommended by the Worldwide Antimalarial Resistance Network (WWARN) (every 4 hours) thus making calculation of parasite clearance half-life difficult. As the trial was designed as a dose-finding study, there was no comparator arm to compare efficacy. We did not find evidence of mature parasites (schizonts) at the two time points

(both ~ 1 hour post -infusion) which would have provided further evidence for de-sequestration by sevuparin. However, the most likely explanation are that schizonts would be cleared very rapidly by the spleen. Future investigation of circulating mature parasites should include assessment during the time of sevuparin infusions.

Overall, these data provide support for a future multi-site randomised controlled Phase II trial, with nested pathophysiological and pharmacokinetic studies. A future trial could generate supportive mechanistic data investigating the magnitude of de-sequestration and invasion-blocking by sevuparin and enable comparison to a control group. This would also provide experimental data to assess associations with laboratory and clinical outcomes to determine expected or unexpected biological mechanisms. For example, parasite adhesion properties have shown to vary between *P. falciparum* isolates from different regions, with some showing high levels of rosetting[31], while others show high levels of organ-specific cytoadhesion e.g. to brain endothelial cells[32]. With an identified maximum tolerated dose, future mechanistic studies alongside a randomised controlled trial would help demonstrate the impact on expected mechanisms and clinical outcomes from this adjunctive therapy.

Conclusion

We have identified the maximum tolerated dose of 3 mg/kg and confirmed the safety of sevuparin as a supportive treatment for future investigation in children with severe malaria.

Methods And Materials

Trial Design

This was a phase I open label safety and dose-finding trial with a primary objective to identify the maximum tolerated dose (MTD) of intravenous sevuparin as an adjunctive therapy in children with severe malaria given as three infusions at 0, 8 and 16 hours. A secondary objective was to assess whether lactate clearance at 8 hours is a realistic and feasible primary endpoint for a subsequent Phase II trial.

The trial used the continual reassessment method to identify the MTD. The continual reassessment method starts with an a priori dose-toxicity curve, reflecting the probability of experiencing a DLT event at the dose received. For this trial we defined a DLT as an APTT > 2.5 times the upper limit of normal (ULN) (grade 3 following the Common Toxicity Criteria v5.0[33]) 1 hour after each dose. The dose-toxicity curve was then re-fitted to the data after each cohort of 2 children was enrolled, based on their observed dose and whether they had a dose limiting toxicity event. After the first 4 children, each subsequent cohort was assigned the next highest dose, until the estimated risk of toxicity was just below or at the target toxicity level, designated as the MTD. The dose limiting toxicity, a priori dose-toxicity curve and chosen target toxicity rate (15%) used in this trial were based upon data shared by the investigators from the adult sevuparin studies in Thailand[27]. We planned to enrol 20 children since this would allow sufficient

data on safety to be generated across a range of doses to identify the MTD from a more informed model relating dose to toxicity events (denoted the 'dose- toxicity' curve) than that available *a priori* based on published data from adult studies.

The protocol for this study has been previously published[34]. Trial registration ISRCTN32271864 (registered on 28/07/2021) and PACTR202007890194806 (registered on 20/07/2020).

Study Population

Children hospitalised with severe malaria were enrolled at Kilifi County Hospital, Kilifi, Kenya and, following a protocol amendment, at Saint Pauls Hospital, Nchelenge Luapula Province, Zambia. Children were eligible for enrolment if they were aged 3 months to 12 years on the day of admission with a slide positive for *P. falciparum* malaria in addition to all of the following: clinical evidence of severe malaria: impaired consciousness: coma (inability to localize painful stimulus) or prostration (inability to sit unsupported for those above 6 months) or deep breathing, a lactate > 2 mmol/L, and a guardian or parent willing and able to provide consent. Children with clinical evidence or a history of a bleeding/coagulation disorder, a comorbidity which clinician believed had a significant risk of poor outcome, e.g. malignancy, end-stage renal failure, major cardiac condition or severe thrombocytopenia (platelet count < 25 $x10^9$/L), were excluded from the trial.

Study Medication

Sevuparin, donated for the trial by the biotech startup Modus Therapeutics, Stockholm Sweden, has been approved for clinical research in Europe and America and remains an investigational drug that is currently in clinical development. The drug product, sevuparin 150 mg/mL solution for intravenous (IV) infusion, was formulated in a 0.015M phosphate buffer at a pH of 7.0 and was stored in a refrigerator at 2–8° celsius and protected from light. The solution for administration was prepared in a syringe (diluted in saline) and kept refrigerated and used within 24 hours.

The trial was open label and clinicians and staff adminstering sevuparin were aware of the dosage. Laboratory staff performing APTT levels were blind to drug dosage level. Children received sevuparin as three infusions (over 5 mins) at 0, 8 and 16 hours after study enrolment. The initial participants (two 'cohorts' of 2 children each, i.e., 4 children in total) received a dose of 1.5 mg/kg/dose with the plan to escalate up to the next highest dose for each cohort of 2 children up to a maximum of 6.0 mg/kg/dose following the recommendations of the continual reassessment model and the Data Monitoring Committee (**Figure S2**).

Outcome measures

The primary outcome was development of a DLT defined as APTT > 2.5 x ULN (grade 3 following the Common Toxicity Criteria v5.0[33]) translating to > 95 seconds (assuming a normal range of 21–38 seconds) 1 hour post sevuparin dose. Secondary outcomes included change in lactate from 0 to 8 hours; presence of mature infected erythrocytes on the blood films at 8 and 24 hours, and parasite clearance

time. Safety endpoints included APTT 24h post enrolment (absolute level and grade), development of abnormalities of coagulation indices (prothrombin) (Grade ≥ 2), neurological sequelae through day 28, mortality through day 28, serious adverse events and Grade 3/4 adverse events through day 28.

Study Screening

Children admitted to the paediatric wards of in Kilifi County and St Pauls Hospital, Nchelenge in Kenya and Zambia respectively with suspected malaria and either coma or deep breathing (defining severe malaria for this Phase I study) were screened by the paediatric triage/admission team for eligibility. When prior written consent from parents or legal guardians could not be obtained, ethics committees approved verbal assent with delayed written informed consent as soon as practical[35]. Otherwise, written informed consent was obtained from parents or guardians before enrolment.

Study Procedures and follow up

The clinical assessments and blood tests taken at admission and during the trial include standard of care and research bloods (**Table S5**). These included admission and serial assessment of full blood count. Lactate (StatStrip® Lactate Meter, NovaBiomedical) was measured at admission, within a window of 5 to 12 hours and within 22 to 26 hours. Malaria parasitaemia was assessed at admission and at 9 hours, 24 hrs and in 12hr intervals until 72 hrs or until a negative slide. APTT was measured at admission (pre dose) and at 1 hour and 9 hours and 24 hours. Samples were stored for future pharmacokinetic assays. Vital signs were clinically reviewed at 1, 2, 4, 8 and 24 hours and then bi-daily until hospital discharge (**Table S5**). Children received parenteral artesunate for at least 3 doses and then followed by an oral course of artemether-lumefantrine per WHO guidelines[36]. All trial patients received intravenous antibiotics. Intravenous maintenance fluids were given at a rate of 4ml/kg/hour until the child was able to drink and retain oral fluids. Antipyretics, anticonvulsants and treatment for hypoglycaemia and other treatments were given according to nationally agreed protocols. Transfusions were provided for children with Hb < 4 g/dl (or Hb < 6 g/dl and respiratory distress (suspected Kussmauls ‘acidotic’ breathing). Any child developing an APTT > 95 seconds (2.5xULN; grade 3 toxicity) did not receive further doses of sevuparin but continued to be followed up. Children were reviewed daily until discharge and followed up at day 7 and day 28. Children lost to follow-up before day 28 were traced for vital status using locator data (permission requested for this data within consent).

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from Imperial College Research Ethics Committee (ICREC) on 13th July 2021 (protocol number 18IC4513), Kenya Scientific and Ethics Review Unit (SERU), Nairobi Kenya on 25th February 2019 (protocol number GCMR-C/127/3744), Imperial College Research Ethics Committee (ICREC) on 13th July 2021 (protocol number 18IC4513) and the Tropical Diseases Research Centre

Ethics Review Committee Ndola, Zambia and National Health Research Ethics Board, Lusaka, Zambia on 24th July 2023 (protocol number NHREB001/24/07/2023). Written informed consent was obtained from parents or legal guardians prior to enrolment, or where previous written consent from could not be obtained, verbal assent was accepted with delayed written informed consent as soon as practicable.

Data management and statistical analysis

Management and outcome data were collected on case report forms. This included bedside observations for clinical parameters, administration of sevuparin, number of transfusions, use of drugs (specifically anticonvulsants, paracetamol, and antibiotics), malaria slide readings, developmental assessment at 28 days, serious adverse events, and date of discharge or in-hospital death.

Mean and standard deviation (sd) was used to estimate change in lactate from baseline at 8 and 24 hours, as well levels of APTT at 24 hours, overall and by dose level. The lactate measurements were taken within a window around each timepoint, namely 5–12 hours for the 8-hour measurement and 22–26 hours for the 24-hour measurement. Geometric mean and 95% confidence intervals were used to describe parasite clearance within 72 hours, estimated using WWARN parasite estimator[37]. The R package bcrm was used to run the continual reassessment model[38]. The dose levels used in the trial were 1.5mg/kg, 3mg/kg, 4mg/kg, 4.5mg/kg, 5mg/kg and 6mg/kg with a-priori risks of a DLT of 0.01, 0.07, 0.1, 0.15, 0.2 and 0.35 respectively. The functional form of the a-priori curve was a power model with Gamma(1,1). The model was set to have no dose skipping during escalation but no restriction during de-escalation. After the first 4 children were dosed at 1.5mg/kg, subsequent children were enrolled in cohorts of 2. After each cohort, recruitment was paused and the DMC reviewed accumulating data on baseline characteristics, sevuparin dosing and APTT levels, any serious adverse events and the model's recommendation for the next dose level. The DMC then gave a recommendation to the site to continue at the chosen dose level.

Consent for publication

Not applicable

Competing interests

No potential conflict of interest relevant to this article was reported.

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Authors Contributions

KM, ASW, DMG, ECG, ND, AD, NO and MC designed the study. MC, JG, PT, SM NO and TNW gathered or generated (laboratory) the data. EO and KM were responsible for trial coordination. ECG and RC analysed the data and ASW verified the data. KM and ECG wrote the first draft article, which all authors commented on. All authors read and approved the final manuscript.

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Data availability

UCL's Innovative CTU supports a controlled access approach based on completion of a data request proforma available from the lead statistician (elizabeth.george@ucl.ac.uk).

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Figures

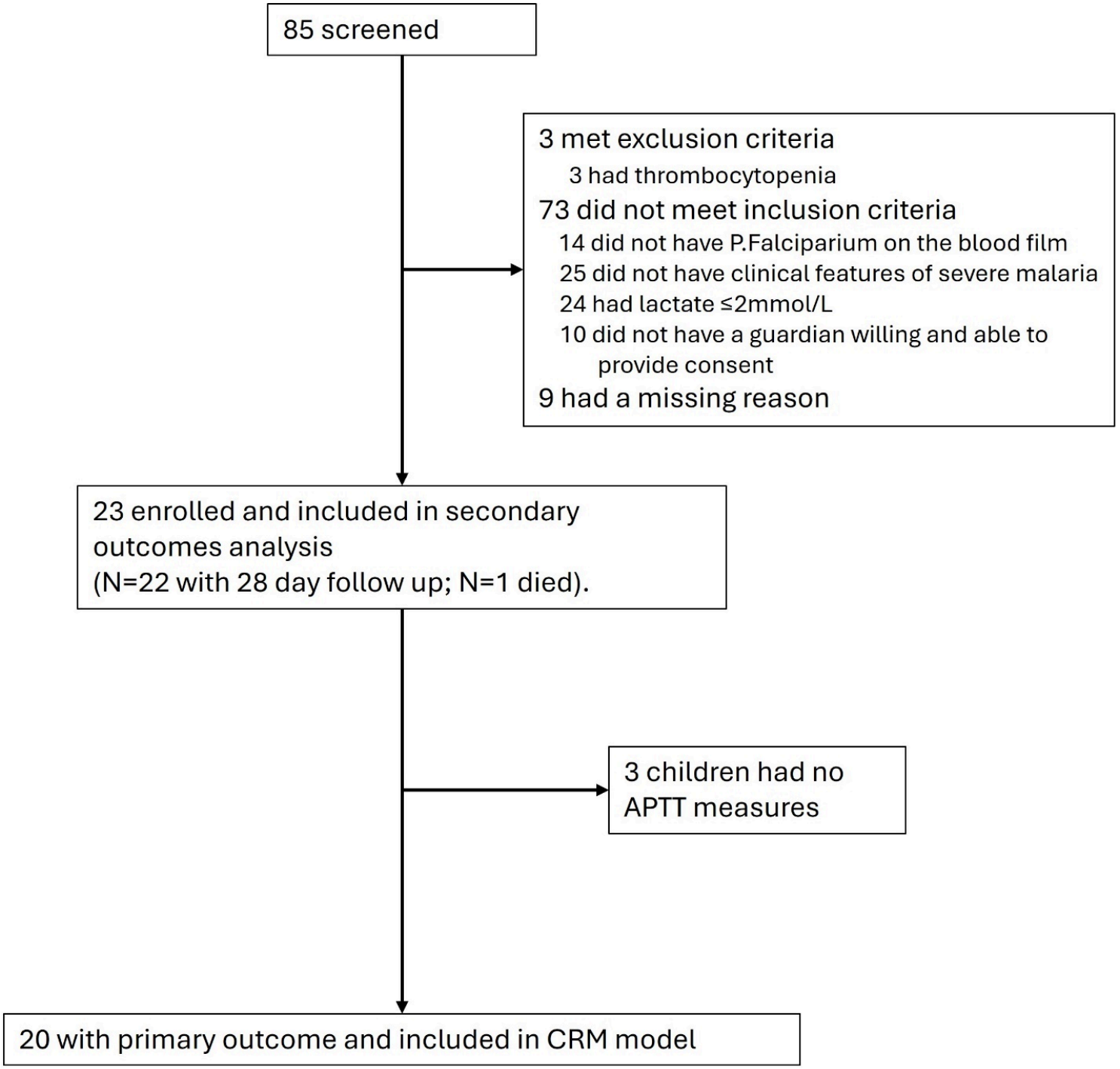


Figure 1

CONSORT diagram

CRM: continuous reassessment model

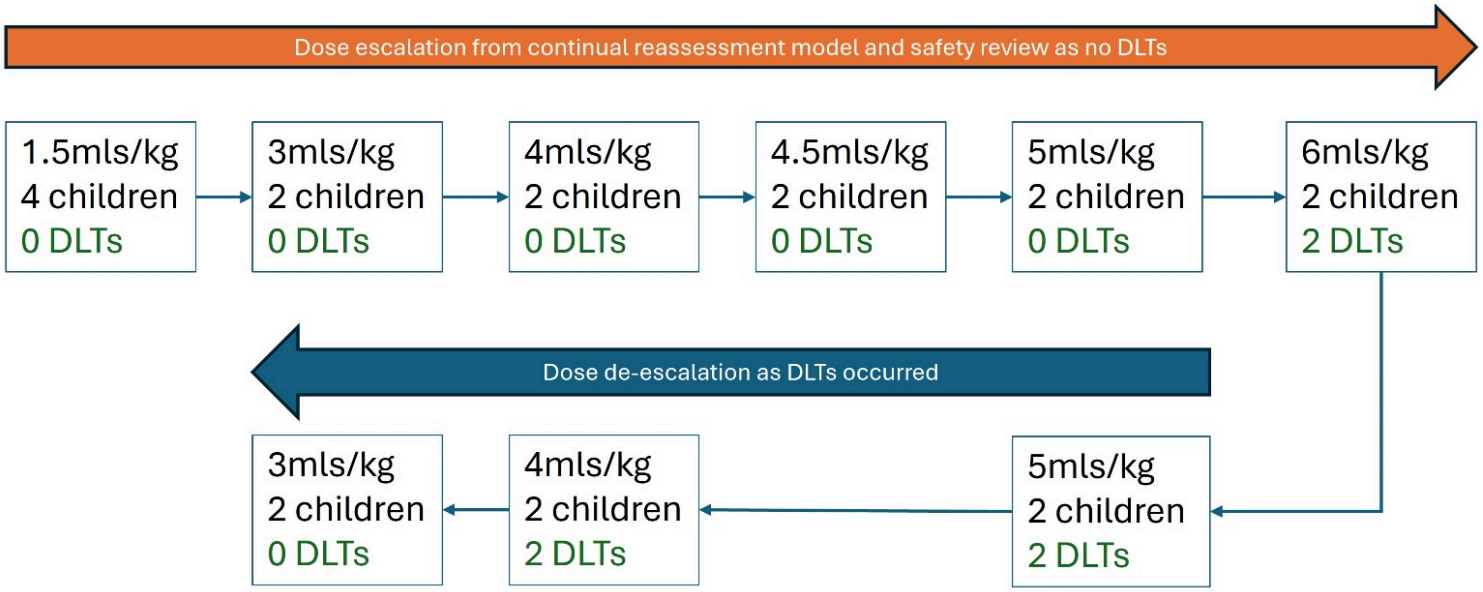
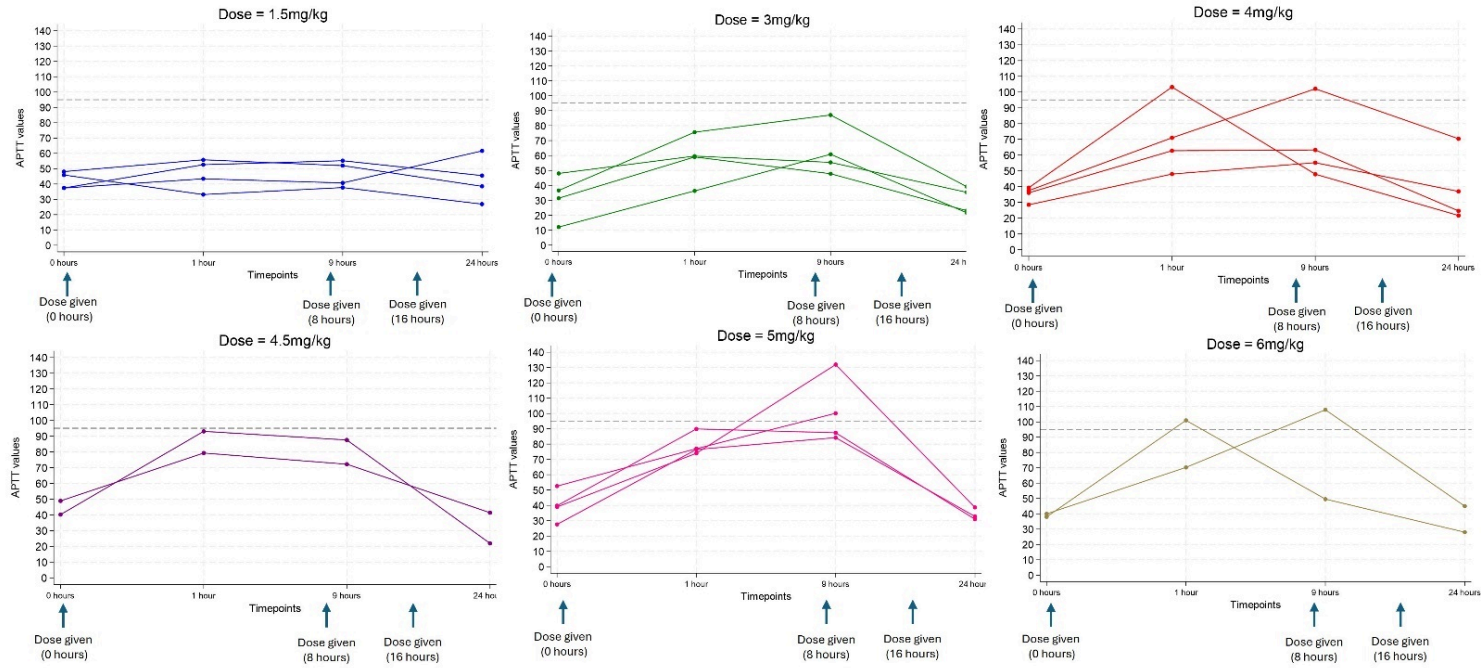


Figure 2

Dose escalations and deescalations in the trial

DLTs: Dose limiting toxicities



Dashed line defines a dose limiting toxicity. If a child had an APTT>95 then they did not receive subsequent doses of Sevuparin

Figure 3

APTT levels in each child

Dashed line defines a dose limiting toxicity. If a child had an APTT>95 then they did receive subsequent doses of sevuparin.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SEVUSMARTSupplementaryappendix8thJune2026.docx
- SEVUSMARTtrialVersion2.128thFeb2023.pdf
- SEVUSMARTSAPv0.2fullysigned.docx
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